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The Ups and Downs of Synapses during Sleep and Learning

Commentary on Aton et al. Sleep promotes cortical response potentiation following visual experience. SLEEP 2014;37:1163-1170.

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In this issue of *SLEEP*, Aton and colleagues report a beautifully designed and executed study that clearly shows that cortical neurons activated by a specific stimulus during wake have increased responsiveness to that stimulus following sleep, but not following an equivalent period of sleep deprivation.[1] Moreover, they show that the magnitude of the increase in responsiveness is proportional to total sleep time (NREM plus REM sleep). The neurons that were studied are in the visual cortex of adult mice, and the stimulus was a grating pattern with a particular orientation. This result seems quite intuitive, in that a neuron that has been trained to respond to a specific stimulus should show an increased responsiveness to that stimulus. And, since there is abundant evidence in animals and humans that both declarative and procedural learning are enhanced during sleep, it seems quite reasonable that the improvements in the cells' responsiveness should be related to sleep occurring between the training and the testing.

The study is important because it provides a direct and discrete test of the seminal and influential hypothesis that a function of sleep is synaptic downscaling. First proposed by Tononi and Cirelli,[2] the synaptic downscaling hypothesis states that synapses are formed and strengthened by experience during wake, and then during sleep, there is global downscaling that relieves the metabolic and spatial burden of the synaptic expansion that occurred during wake. Since this downscaling is global, it spares the strongest and most important synapses. Hence, the learning process during sleep is seen as a weeding out of the insignificant and therefore a relative strengthening of the significant. Although the hypothesis initially seemed too simplistic to be true, many studies have been done that lend support to it.[3-6] However, what has been lacking are experimental designs with the potential of disproving the hypothesis, and that is what the current paper by Aton et al.[1] presents. The form of plasticity they studied is considered an *in vivo* form of Hebbian long-term synaptic (LTP) potentiation. This is because it satisfies basic criteria for Hebbian LTP (e.g., input specificity) and is governed by the same intracellular mechanisms that govern LTP *in vitro*. It also involves *only* a gain of synaptic response to the experienced stimulus—as responses to other stimuli are unchanged.[7] This means that the results of Anton showing that the responsiveness of specific neurons that respond to a specific modality of stimulation are strengthened during sleep, and not just spared. These results are contrary to the synaptic downscaling hypothesis.

Other results also indicate that selected synapses are strengthened during sleep. A prime example is the reorganization of synaptic connections in the visual cortex following monocular deprivation in the kitten.[8] These dramatic changes, including selective losses as well as gains, were shown to depend on sleep. The most dramatic case of synapse formation during sleep was seen in ground squirrels recovering from bouts of hibernation.[9] During the bout, as much as 30% of dendritic structure and synapses can be lost in certain regions of the brain. This structure and the related synapses are restored in 3 to 4 hours during which the animal is mostly in very deep NREM sleep as indicated by high EEG delta power.

Does the study by Aton completely disprove the synaptic downscaling hypothesis? Certainly not. Taking all of the evidence into consideration, the reasonable conclusion is that during sleep there is both synaptic downscaling and synaptic strengthening. Surely the demonstrated functions of sleep in consolidating long-term memory must require synaptic strengthening in specific regions and specific circuits. But an important function of sleep can also be the cleaning out of the short term memory stores—as originally proposed many years ago.[10,11] It is significant that the studies that have produced results that contradict the downscaling hypothesis (the hibernation case being the exception) have focused on cells and circuits involved in plasticity in specific responses. In contrast, the studies seen as supporting the downscaling hypothesis have mostly measured global changes. It is reasonable to expect that during the sleep phase, many more weak and unimportant synapses would have to be eliminated than important synapses representing information transfer into long term memory would be strengthened.

Direct evidence for selective memories being strengthened during sleep, and therefore presumably involving synaptic strengthening, comes from both animal and human studies in which specific memories are reactivated during sleep and then shown to be stronger during subsequent wake. Rolls et al.[12] paired foot shock with an odor cue. When the animal was re-exposed to the conditioned odor during sleep, the subsequent freezing response to that odor during wake was much increased. In contrast, if the animals received microinjections of a protein synthesis inhibitor prior to their sleep phase and re-exposed to the conditioned odor during sleep, their subsequent freezing response to the conditioned stimulus during wake was much diminished. An interpretation of these results is that reactivation and therefore re-consolidation of memory during sleep strengthens the synaptic connections responsible for that memory, but if that process of reconsolidation is blocked, the memory is weakened.

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Strengthening of memories by reactivation during sleep has also been shown in humans. Humans were trained to recognize the location of pairs of symbols on a screen and then retested after a sleep phase. If they were trained in association with an odor cue, and that odor cue was introduced during NREM sleep, the subsequent recall as greater than if there had been no conditioned odor cue, and also greater than when the conditioned odor cue re-exposure was during wake or during REM sleep.[13] These results also support the idea that learning takes place when memories are re-activated and re-consolidated during sleep resulting in increased synaptic strengths.

A similar human memory experiment used sounds instead of smells. Once again, subjects learned the positions of pairs of symbols on a grid. However, each pair was associated with a characteristic sound: bell–ding, cat–meow, etc. Only half of the sounds were reintroduced during sleep, and the following day, the performance of the subjects on the pairs that were cued during sleep was greater.[14]

Learning and memory involve many processes: encoding of experience, consolidation of memory transcripts into long term stores, integration of those transcripts with the existing knowledge base, and the ability to recall memories and apply them to new situations. It is inconceivable that the demonstrated role of sleep in these processes does not involve strengthening of synapses in selective cells and circuits, and that is exactly what is demonstrated in the paper by Aton et al.[1]

CITATION

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DISCLOSURE STATEMENT

The author has indicated no financial conflicts of interest.

REFERENCES

1. Aton SJ, Suresh A, Broussard C, Frank MG. Sleep promotes cortical response potentiation following visual experience. Sleep 2014;37:1163-70.
2. Tononi G, Cirelli C. Sleep and synaptic homeostasis: a hypothesis. Brain Res Bull 2003;62:143-50.
3. Vyazovskiy VV, Cirelli C, Pfister-Genskow M, Faraguna U, Tononi G. Molecular and electrophysiological evidence for net synaptic potentiation in wake and depression in sleep. Nat Neurosci 2008;11:200-8.
4. Maret S, Faraguna U, Nelson AB, Cirelli C, Tononi G. Sleep and waking modulate spine turnover in the adolescent mouse cortex. Nat Neurosci 2011;14:1418-20.
5. Liu ZW, Faraguna U, Cirelli C, Tononi G, Gao XB. Direct evidence for wake-related increases and sleep-related decreases in synaptic strength in rodent cortex. J Neurosci 2010;30:8671-5.
6. Yang G, Gan WB. Sleep contributes to dendritic spine formation and elimination in the developing mouse somatosensory cortex. Dev Neurobiol 2012;72:1391-8.
7. Cooke SF, Bear MF. Stimulus-selective response plasticity in the visual cortex: An assay for the assessment of pathophysiology and treatment of cognitive impairment associated with psychiatric disorders. Biol Psychiatry 2012;71:487-95.
8. Frank MG, Issa NP, Stryker MP. Sleep enhances plasticity in developing visual cortex. Neuron 2001;30:275-87
9. Von der Ohe CG, Darian-Smith C, Garner CC, Heller HC. Ubiquitous and temperature-dependent neural plasticity in hibernators. J Neurosci 2006;26:10590-8
10. Crick F, Mitchison G. The function of dream sleep. Nature 1983;198:111-4.
11. Giuditta A. The sequential hypothesis of the function of sleep. Behav Brain Res 1995;69:157-66.
12. Rolls A, Makam M, Kroeger D, Colas D, de Lecea L, Heller HC. Sleep to forget: interference of fear memories during sleep. Mol Psychiatry 2013;18:1166-70.
13. Rasch B, Buchel C, Gais S, Born J. Odor cues during slow-wave sleep prompt declarative memory consolidation. Science 2007;315:1426-9
14. Rudoy JD, Voss JL, Westerberg CE, Paller KA. Strengthening individual memories by reactivating them during sleep. Science 2009:326;1079.